Remarks

Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 are pending in the application. Claims 10, 21, and 29 have been canceled without prejudice. Claims 1, 9, 23-25, and 26 have been amended.

Claims 10 and 21 have been canceled in light of the amendment to claim 1. Claim 29 was canceled because it was rendered redundant by the amendment to claim 26.

Claim 1 was amended to restrict the definition of R_3. Claims 9 and 23-25 were amended to reflect the changes to claims 1. Claim 26 was amended to incorperate the limitations of claims 1 and 29.

Importantly, support for the claim amendments can be found throughout the application. Therefore, no new matter has been added. Moreover, the claim amendments should not be construed to be an acquiescence to any of the claim rejections. Rather, the amendments to the claims are being made solely to expedite the prosecution of the above-identified application. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Claim Rejections Based on 35 USC § 102(b)

Various sets of claims were rejected under 35 USC 102(b), based on the Examiner's contentions that they are anticipated by various patents and publications. To better organize the Applicant's traverses of the Examiner's rejections under 35 USC 102(b), they are set forth below in paragraphs numbered corresponding to the numbering scheme used in the outstanding Final Office Action.

2. Claims 1-4, 7-10, 12-16, 18, 20-21, and 28 were rejected under 35 USC § 102(b), based on the Examiner's contention that they are anticipated by WO 92/02256. Specifically, the Examiner contends that the reference "discloses cyclodextrin complexes containing fentanyl, alfentanil, sufentanil, and lofentanil for the treatment of pain."

Claims 1-25

In order to expedite prosecution, the Applicants have amended claim 1, removing hydrogen from the definition of R_3, such that fentanyl no longer falls within the scope of claim1. Likewise, the Applicants respectfully point out that alfentanil, sufentanil, and lofentanil do not fall within the scope of amended claim 1. Alfentanil and sufentanil do not fall within the scope of claim 1 because R_4 is limited to aryl; whereas, alfentanil and sufentanil have a heteroaryl moiety at that position. Lofentanil does not fall within the scope of claim 1 because lofentanil contains a methyl group attached to the 3-position of the piperidine ring. Therefore, the Applicants contend that amended claim 1 and subsequent dependent claims are not anticipated by WO 92/02256 because fentanyl, alfentanil, sufentanil, and lofentanil do not fall with the scope of amended claim 1 or subsequent dependent claims.

Claims 26-29

In light of the amendment to claim 1, claim 26 was amended to include generic structure **A** and the attendant definitions. The amendment does not consitute the addition of new matter because original claim 26 was dependent on claim 1.

With respect to the Examiner's rejection of claim 28 based on WO 92/02256, the Applicants have amended claim 26 to include the limitation of dependent claim 29, i.e., that the formulation is orally administered. This amendment impacts claim 28 because it is dependent on claim 26. Importantly, this amendment does not the addition of constitute new matter because original claim 29 was dependent on claims 26, 27, and 28. Of course, dependent claim 29 was canceled because it was rendered redundant by the amendment of claim 26.

The Applicants respectfully assert that WO 92/02256 does not provide any examples of oral administration. In addition, the Applicants respectfully remind the Examiner that "a claim is anticipated only if each and every element as set forth in the claim, either expressed or inherently described, is found in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applying this standard, the Applicants respectfully assert that WO 92/02256 does not anticipate dependent claim 28 which requires *oral* administration.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of under 35 USC 102(b) based on the WO 92/02256 reference.

3. Claims 1, 3, 7-10, 12-16, 18, 20-21, 23-26, and 28 stand rejected under 35 USC § 102(b), based on the Examiner's contention that they are anticipated by U.S. Pat. No. 5,451,408 ("the '408 patent"). Specifically, the Examiner contends that the reference "discloses liposomal formulations containing fentanyl for the treatment of pain."

Claims 1-25

As noted above, in order to expedite prosecution, claim 1 has been amended so that fentanyl does not fall within the scope of amended claim 1 or any claims dependent thereon. Therefore, the Applicants contend that the '408 patent does not anticipate claim 1 or dependent claims. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 1, 3, 7-9, 12-16, 18, 20, 23-25 under 35 USC 102(b) based on the '408 patent.

Claims 26-29

Regarding the Examiner's rejection of claims 26 and 28 based on the '408 patent, the Applicants respectfully contend that the amended claims are not anticipated by the '408 patent because claims 26 and 28 require oral administration of the formulation. In contrast, the '408 patent only provides examples for pulmonary administration of liposome-encapsulated opioids. *See, e.g.,* US 5,451,408, column 3, lines 55-60. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26 and 28 under 35 USC 102(b) based on the '408 patent.

4. Claims 1, 3-4, 7-10, 12-16, 18, 20-21, 23-26, and 28 stand rejected under 35 USC § 102(b), based on the Examiner's contention that they are anticipated by Lee et al. (WO 99/36071). Specifically, the Examiner reasons that "WO discloses fentanyl and fentanyl derivatives in polymeric carriers."

Claims 1-25

As noted above, claim 1 has been amended to remove hydrogen from the Markush group defining R_3 of structure **A**. Therefore, claim 1 does not encompass the compounds (fentanyl, benzylfentanyl, sufentanil, thiofentanyl, beta-hydroxyfentanyl, alfentanyl, and lofentanyl) used in

the examples of WO 99/36071. Accordingly, the Applicants respectfully request the withdrawal of the rejections under 35 USC 102(b) based on WO 99/36071.

Claims 26-29

With respect to the Examiner's rejection of claims 26 and 28 based on WO 99/36071, the Applicants contend that the amendedment to claim 26 discussed above places claims 26 and 28 in condition for allowance. Claim 26 has been amended to require that the formulation be administered orally to a mammal. In contrast, the Lee reference does not give any examples of administration to a mammal. The Lee reference only gives the drug release profile in a PBS solution. *See* Figures 1, 2, and 3. Therefore, the Applicants respectfully contend that WO 99/36071 does not form the basis of a proper anticipation rejection of claims 26 and 28 because the Lee reference does not teach each and every claim element. *See Verdegaal Bros.*, 814 F.2d at 631. teach provide examples of oral administration of the formulation. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26 and 28 under 35 USC 102(b) based on WO 99/36071.

Claim Rejections Based on 35 USC § 103(a)

Various sets of claims were rejected under 35 USC 103(a), based on the Examiner's contentions that they are unpatentable over various patents and publications. To better organize the Applicant's traverses of the Examiner's rejections under 35 USC 103(a), they are set forth below in paragraphs numbered corresponding to the numbering scheme used in the Final Office Action.

6. Claims 1-4, 7-10, 12-16, 18, 20-21, and 23-29 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 92/02256. Specificially, the Examiner contends that "it is deemed obvious to one of ordinary skill in the art to encapsulate any compound based on the basic structure of fentanyl in the cyclodextrin compositions of WO with a reasonable expectation of success." The Applicants respectfully traverse.

The Applicants respectfully contend that one of ordinary skill of the art would not have a reasonable expectation of success in a program focused on *oral* adminstration of a formulation

for the treatment of pain, which formulation comprises cyclodextrins and fentanyl or structurally related compounds. In support of this contention, the Applicants respectfully direct the Examiner to Mezei ('408 patent), stating at column 2, line 30 that "blood plasma levels [of opioids] obtained from oral preparations show wide variability." Thus, one of ordinary skill in the art would reasonably presume that oral formulations of fentanyl would provide a substandard analgesic treatment.

In contrast, the Applicants have demonstrated in Example 1 that oral formulations comprising fentanyl and a cyclodextrin exhibit unexpectedly good analgesic treatment compared to saline solutions of fentanyl in oral administration. Hence, the Applicants respectfully contend that one of ordinary skill in the art, armed only with the teachings of WO 92/02256, would not have had a reasonable expectation of success in a program directed toward the development of orally-bioavailable formulations of the compounds defined in the claims. Accordingly, the Applicants respectfully request the withdrawal of the claims rejection under 35 USC § 103(a) based on the WO 92/02256 reference.

7. Claims 1-4, 7-10, 12-16, 18, 20-21, and 23-29 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 92/36071. Specifically, the Examiner contends that the "mode of administration is deemed to be a manipulatable parameter and the choice of the practitioner of the art to obtain the best possible results."

Claims 1-25

In regards to the Examiners rejection of claims 1-4, 7-10, 12-16, 18, 20-21, and 23-25, the Applicants have amended the claims as discussed above. The WO 92/36071 reference does not teach any of the compounds that fall within the scope of claim 1. Furthermore, the WO 92/36071 reference does not suggest or motivate one of ordinary skill in the art to prepare formulations of any of the compounds in the formulations of claim 1.

Claims 26-29

Regarding the Examiner's rejection of claims 26-29, the Applicants respectfully traverse that one of ordinary skill in the art would not have a reasonable expectation of success in a

program for oral administration of opioids. As discussed above, the Mezei ('408 patent) reference states at column 2, line 30 that "blood plasma levels [of opioids] obtained from oral preparations show wide variability." Thus, one of ordinary skill in the art would reasonably presume that oral formulations of fentanyl or its derivates would not provide effective analgesic treatment. Accordingly, the Applicants respectfully request the withdrawal of the claims rejection under 35 USC § 103(a) based on the WO 92/36071 reference.

Request for Withdrawal of Premature Final Rejection

The Applicants respectfully request withdrawal of the Final Rejection in the outstanding Office Action. Specifically, the Applicants contend that the finality of the Office Action was inappropriate because the Examiner introduced a new grounds of rejection based on WO 99/36071.

In connection with the aforementioned rejection, the Examiner states that "WO discloses fentanyl and fentanyl derivates in polymeric carriers." The subject matter "fentanyl" and "polymeric carriers" was in claim 1 as originally filed. Hence, the rejection on the grounds of WO 00/36071 could have been made in the first Office Action; in other words, the rejection wass not made on the basis of a claim amendment. In addition, WO 99/36071 was not listed on the Information Disclosure Statement. The MPEP states "under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)." MPEP § 706.07(a). Accordingly, the Applicants request withdrawal of the Final Rejection.

Fees

The Applicants believe no fee is due in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any required fee to our Deposit Account, **06-1448**.

Conclusion

In view of the above amendments and remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
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